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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/581,402 06/12/00 FUJISAWA

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HM12/1108

EXAMINER

FREDMAN, J

ART UNIT

PAPER NUMBER

1655

DATE MAILED:

11/08/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/581,402

Applicant(s)

Fujisawa et al

Examiner

Jeffrey Fredman

Art Unit

1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Oct 5, 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above, claim(s) 8-11 and 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 12, and 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☒ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892) 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 19) ☐ Notice of Informal Patent Application (PTO-152)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3, 4 20) ☐ Other:

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DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-7, 12 and 13 in Paper No. 6 is acknowledged. Applicant's election of the species of compound 65 as shown below is acknowledged.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-7, 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds shown in Tables 1-3, does not reasonably provide enablement for the entire genus of structures which are potential matrix metalloproteinase inhibitors encompassed by the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The nature of the invention is chemical, in an area where single structural substitutions may alter the function of the compound in unpredictable ways. The claimed invention is drawn broadly to any compound which falls within the genus disclosed by claim 1. While the specification provides substantial guidance on methods of making the chemical compounds and some guidance on the use of the working examples, a particular 40 or so compounds disclosed in

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tables 1-3 on pages 148-152 of the specification, the specification gives no guidance on the use of any compound outside of this set of compounds with regard to their function or efficacy. As noted, there are about 40 working examples. The prior art recognizes the extreme unpredictability in this area. In fact, Dickens et al (WO 94/02447), synthesizing extremely similar compounds states regarding his compounds that "It has been found that such compounds have in general the sought after but unpredictable combination of desirable formulation characteristics, including water-solubility, as well as desirable activity profiles as inhibitors of MMP's (page 4)". Dickens further notes that "Unfortunately, however, the physicochemical and/or pharmacokinetic properties of the specific compounds disclosed in those publications have generally been disappointing (page 2 last sentence to page 3)". Thus, Dickens notes that 12 different patents and published patent applications synthesized particular compounds, not simply a disclosure as here of broad generic structures, and these particular compounds were unpredictable in function and unable to achieve the sought after purpose of treatment. Further evidence of the unpredictability is provided by Brenner (WO 97/05865) who notes that it is desirable to identify inhibitors, but (prior to his work) "none of the inhibitors so far identified has proven an effective therapeutic for the treatment of collagen related diseases or even an inhibitor to C-proteinase activity (page 5, lines 2-4)". Crimmin et al (U.S. Patent 5,652,262) is currently cumulative over the Dickens prior art, but Crimmin teaches similar compounds and the unpredictability of such compounds (see column 2, lines 40-44). As shown by the art, this area is highly unpredictable and alteration of the compounds results in altered activities and altered formulation profiles which have entirely

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unpredictable results. It would require a very large amount of experimentation, amounting to the synthesis of a large number of representative compounds, followed by testing the compounds for activity in order to determine whether particular subelements of the genus claim are useful in metalloproteinase inhibitor assays. This amount of experimentation is not only inventive, but is sufficient to provide the material for multiple Ph.D theses and would be very expensive and time consuming. Therefore, given the unpredictability of the art, the teachings in the art that this area is highly unpredictable, the broad claims, the large amount of experimentation necessary and the minimal guidance presented of essential elements which are required for function as opposed to 40 working examples and the relatively high level of skill in the art, it is concluded that, on balancing these factors, undue experimentation would be required to use the invention as claimed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

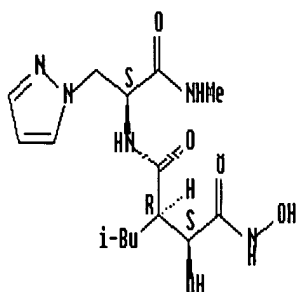
A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-7, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Dickens et al (WO 94/02447).

Dickens teaches a compound with the structure shown in example 6 (page 24, example 6).

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This compound of Dickens in example 6 anticipates the compound of formula I, in claim 1, since it comprises a situation where R1 and R2 are Hydrogen, R3 is hydroxy, R4 is a butyl group, R5 is hydrogen and R6 is methyl, R7 and R8 are Hydrogen and R9 is a form of a substituted alkylene. Dickens further teaches that R5 can be a lower alkyl (as required by claims 2-3 and 12-13), all the other elements can be the same. The Dickens compound R9 is a ring, but has an amino group and a unsaturated alkyl chain within the group, which meets the requirements of claim 3. Dickens teaches that the compounds are matrix metalloproteinase inhibitors (abstract) and teaches pharmaceutically and veterinarily acceptable excipients and carriers (page 13). The Dickens compound has TNF activity (page 4).

Allowable Subject Matter

6. The elected species, Compound 65, is novel and unobvious over the cited prior art, because none of the art teaches or suggests it's particular structure.

Conclusion

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7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Crimmin et al (U.S. Patent 5,652,262) is currently cumulative over the Dickens prior art, but Crimmin teaches similar compounds and the unpredictability of such compounds.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the early morning or the afternoon are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).


Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

November 7, 2001